



## **64Cu-DOTATATE PET for Neuroendocrine Tumors: a Prospective Head-to-Head Comparison with 111In-DTPA-octreotide in 112 Patients**

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# <sup>64</sup>Cu-DOTATATE PET for Neuroendocrine Tumors: A Prospective Head-to-Head Comparison with <sup>111</sup>In-DTPA-Octreotide in 112 Patients

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Neuroendocrine tumors (NETs) can be visualized using radio-labeled somatostatin analogs. We have previously shown the clinical potential of <sup>64</sup>Cu-DOTATATE in a small first-in-human feasibility study. The aim of the present study was, in a larger prospective design, to compare on a head-to-head basis the performance of <sup>64</sup>Cu-DOTATATE and <sup>111</sup>In-diethylenetriaminepentaacetic acid (DTPA)-octreotide (<sup>111</sup>In-DTPA-OC) as a basis for implementing <sup>64</sup>Cu-DOTATATE as a routine. **Methods:** We prospectively enrolled 112 patients with pathologically confirmed NETs of gastroenteropancreatic or pulmonary origin. All patients underwent both PET/CT with <sup>64</sup>Cu-DOTATATE and SPECT/CT with <sup>111</sup>In-DTPA-OC within 60 d. PET scans were acquired 1 h after injection of 202 MBq (range, 183–232 MBq) of <sup>64</sup>Cu-DOTATATE after a diagnostic contrast-enhanced CT scan. Patients were followed for 42–60 mo for evaluation of discrepant imaging findings. The McNemar test was used to compare the diagnostic performance. **Results:** Eighty-seven patients were congruently PET- and SPECT-positive. No SPECT-positive cases were PET-negative, whereas 10 false-negative SPECT cases were identified using PET. The diagnostic sensitivity and accuracy of <sup>64</sup>Cu-DOTATATE (97% for both) were significantly better than those of <sup>111</sup>In-DTPA-OC (87% and 88%, respectively,  $P = 0.017$ ). In 84 patients (75%), <sup>64</sup>Cu-DOTATATE identified more lesions than <sup>111</sup>In-DTPA-OC and always at least as many. In total, twice as many lesions were detected with <sup>64</sup>Cu-DOTATATE than with <sup>111</sup>In-DTPA-OC. Moreover, in 40 of 112 cases (36%) lesions were detected by <sup>64</sup>Cu-DOTATATE in organs not identified as disease-involved by <sup>111</sup>In-DTPA-OC. **Conclusion:** With these results, we demonstrate that <sup>64</sup>Cu-DOTATATE is far superior to <sup>111</sup>In-DTPA-OC in diagnostic performance in NET patients. Therefore, we do not hesitate to recommend implementation of <sup>64</sup>Cu-DOTATATE as a replacement for <sup>111</sup>In-DTPA-OC.

**Key Words:** neuroendocrine tumors; cancer; somatostatin receptor imaging; <sup>64</sup>Cu-DOTATATE; <sup>111</sup>In-DTPA-octreotide; PET; PET/CT; SPECT; molecular imaging; prospective

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In well-differentiated neuroendocrine tumors (NETs), somatostatin receptors are consistently overexpressed (1–3). This key feature of NETs may be visualized using radiolabeled somatostatin receptor ligands and SPECT or PET. Still, <sup>111</sup>In-diethylenetriaminepentaacetic acid (DTPA)-octreotide is considered the standard method according to current international guidelines (4,5). However, because of the better sensitivity, spatial resolution, and inherently quantitative nature of PET, somatostatin receptor imaging (SRI) with PET is increasingly used. Most common is the use of the <sup>68</sup>Ga-labeled somatostatin analogs, for example, <sup>68</sup>Ga-DOTATATE (6–9), <sup>68</sup>Ga-DOTATOC (10–12), and <sup>68</sup>Ga-DOTANOC (13). However, the high positron energy of <sup>68</sup>Ga limits spatial resolution and the short half-life of 68 min may be challenging logistically, because production has to be aligned with patients and to be repeated several times a day.

To overcome some of these challenges, we recently introduced <sup>64</sup>Cu-DOTATATE, which has a long half-life of 12.7 h and can be produced as a once-daily batch with a shelf life of more than 24 h (14). These advantages of <sup>64</sup>Cu-DOTATATE make it possible to produce the tracer in a central location and distribute it to local PET centers. The positron energy of <sup>64</sup>Cu is also much lower than that of <sup>68</sup>Ga and therefore should translate into better spatial resolution (Table 1). In addition, by choosing the octreotate peptid for this tracer, we have a better match for the commonly used therapy ligand <sup>177</sup>Lu-DOTATATE, enabling accurate diagnostic imaging of the organs treated with <sup>177</sup>Lu-DOTATATE.

The use of DOTA as a chelate has been challenged in several studies (15,16). However, we demonstrated in our phase I study sufficient in vivo stability of the <sup>64</sup>Cu-DOTA complex to obtain good-quality images (14), which we have also confirmed in pre-clinical studies comparing DOTA with other chelates (17–19). Data from our first-in-human study of 14 patients demonstrated that

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**TABLE 1**  
Characteristics of Somatostatin Receptor Radiotracers

Characteristic	<sup>111</sup> In-DTPA-OC	<sup>68</sup> Ga-DOTATATE, <sup>68</sup> Ga-DOTATOC, <sup>68</sup> Ga-DOTANOC	<sup>64</sup> Cu-DOTATATE
Radionuclide from	Cyclotron	Generator	Cyclotron
Physical half-life	2.8 d	68 min	12.7 h
Positron range			
Mean in water	—	≈3 mm	<1 mm
Maximum in water	—	≈8 mm	≈3 mm
Radiation dosimetry*	5.6–11.1 mSv	2.0–5.1 mSv	5.7–6.9 mSv
Tracer labeling	Locally (kit)	Locally	Centrally (or locally)
Shelf life of labeled compound†	6 h	3 h	24 h
Delayed imaging (>3 h)	Possible	Not possible	Possible

\*From Johnbeck et al. (36).

†<sup>111</sup>In-DTPA-OC: according to manufacturer's instruction; <sup>68</sup>Ga: limited by half-life of isotope to obtain 1 patient dose (new generator); and <sup>64</sup>Cu-DOTATATE: as approved by Danish Health and Medicines Authority.

imaging was feasible using an activity of 200 MBq, with a favorable dosimetry of only 6.3 mSv (14). Compared with conventional SRI using <sup>111</sup>In-DTPA-octreotide (<sup>111</sup>In-DTPA-OC), additional lesions were detected in 6 of 14 patients and 5 of these additional lesions were found in organs not previously known as metastatic. In the same study, we also found that PET could be performed between 1 and 24 h, and we selected the 1-h time point for routine use. Taken together, data from our previous study allowed us to establish a standardized protocol for <sup>64</sup>Cu-DOTATATE in NET.

The aim of the present study was therefore, on a larger scale, to perform a prospective study comparing on a head-to-head basis in 112 NET patients the performance of <sup>64</sup>Cu-DOTATATE and <sup>111</sup>In-DTPA-OC as a basis for implementing <sup>64</sup>Cu-DOTATATE as a routine. To evaluate discrepant findings, patients were followed for 42–60 mo after the 2 scans were obtained.

## MATERIALS AND METHODS

### Patients and Inclusion Criteria

Eligible patients had histopathologically confirmed NETs of gastroenteropancreatic or pulmonary origin of all grades (20). They were enrolled in the study from November 2009 to May 2011, and follow-up ended on November 15, 2014, for evaluation of discrepant imaging findings. Accordingly, patients were followed for 42–60 mo. Patients were offered study inclusion in the case of referral to conventional SRI with <sup>111</sup>In-DTPA-OC as part of their routine examinations. <sup>64</sup>Cu-DOTATATE PET and <sup>111</sup>In-DTPA-OC SPECT were performed within a maximum of 60 d (mean, 24 d) in a random order. The study group consisted of 63 (56%) men and 49 (44%) women with a mean age of 62 y (range, 30–84 y) (Table 2).

All patients gave written informed consent before inclusion. The study was approved by the Regional Scientific Ethical Committee (reference no. H-D-2008-045).

### Radiotracer, Image Acquisition, and Reconstruction

**Radiotracers.** <sup>64</sup>Cu-DOTATATE was produced in-house as previously described (14). The labeling efficiency was greater than 95% (determined with radio-reversed-phase high-performance liquid chromatography), and the specific activity was 4.78 MBq/mmol. <sup>111</sup>In-DTPA-OC was purchased from Covidien and prepared in accordance with the instructions of the manufacturer.

**PET/CT.** All patients were PET-scanned using a Biograph 64 TruePoint PET/CT scanner (Siemens Medical Solutions) with an axial field of view of 216 mm and a transaxial field of view of 205 mm. Axial and transaxial resolutions were 4.7 and 4.2 mm, respectively. Emission scans were acquired 1 h after injection of 183–232 (mean, 202) MBq of <sup>64</sup>Cu-DOTATATE, with an average of 44.6 mmol (40.2–50.9 mmol) of octreotate administered per dose. Whole-body PET scans (skull to mid thigh) were obtained in 3-dimensional mode, with an acquisition time of 3 min per bed position. PET data were reconstructed with the TrueX (Siemens Medical Solutions) algorithm using 3 iterations and 21 subsets and smoothed by gaussian filter (full width at half maximum, 2 mm). CT data were used for attenuation correction. Before the PET scan, a diagnostic CT scan was obtained with 3-mm slice thickness, 120 kV, and a quality reference of 225 mAs modulated by the Care Dose 4D automatic exposure control system (Siemens Medical Solutions). Unless contraindicated, 75 mL of iodine-containing contrast agent were administered using an automatic infusion system (Optiray 300; Covidien), with scan delays of 60 s (flow rate, 1.5 mL/s), followed by an infusion of 100 mL of NaCl (flow rate, 2.5 mL/s). Furthermore, patients had been asked to drink 500 mL of water 25 min before image acquisition. PET and CT images were fused and reviewed on a dedicated workstation.

**SPECT/CT.** Planar and tomographic images were acquired using dual-head hybrid SPECT/CT cameras (Precedence 16-slice scanner [Philips Healthcare]; VG Hawkeye [GE Healthcare]) after intravenous administration of 181–268 (mean, 218) MBq of <sup>111</sup>In-DTPA-OC. Whole-body planar images (anterior and posterior, scan speed 5 cm/min, 512 × 1,024 matrix) were acquired at 24 h after injection and at 48 h after injection if relevant (15-min static planar image [256 × 256 matrix] of the abdomen using a large-field-of-view medium-energy collimator). During the same session, SPECT over the abdomen or chest per indication (20 s/step, 128 angles, 128 × 128 matrix) was performed. A low-dose CT (20 mA, 140 kV [Precedence] or 2.5 mA, 140 kV [Hawkeye]) was used as an anatomic guide and for attenuation correction. Scatter correction was used, and SPECT and CT were fused and reviewed on dedicated workstations (EBW [Philips Healthcare]; eNTEGRA [GE Healthcare]).

### Visual Image Analysis and Activity Quantification

PET/CT and SPECT/CT were analyzed separately by 2 different teams consisting of 2 experienced interpreters. The 2 teams were masked to the images and readings of the other team. There had to

**TABLE 2**  
Characteristics of Study Population (*n* = 112)

Characteristic	<i>n</i>
<b>Sex</b>	
Male	63 (56%)
Female	49 (44%)
Mean age (y)	62 (range, 30–84)
<b>Site of primary tumor</b>	
Lung carcinoid	9 (8%)
NET of unknown primary site origin	23 (21%)
Gastric NET	1 (1%)
Small intestinal NET	49 (44%)
Pancreatic NET	19 (17%)
NET originated from cecum/appendix	6 (5%)
NET originated from the rectum	2 (1.5%)
NET originated from extrahepatic biliary tract	2 (1.5%)
NET originated from the esophagus	1 (1%)
<b>Functional status</b>	
Nonfunctioning	72 (64%)
Functioning	40 (36%)
Carcinoid syndrome	35 (31%)
Gastrinoma	4 (3.6%)
Glucagonoma	1 (0.9%)
<b>Grade (World Health Organization)*</b>	
Low-grade (G1) Ki-67, ≤2%	31 (28%)
Intermediate-grade (G2) Ki-67, 3%–20%	70 (62%)
High-grade (G3) Ki-67, >20%	9 (8%)
Ki-67 index not available	2 (2%)
<b>Primary removed?</b>	
Yes	52 (46%)
No	60 (54%)
<b>Previous treatment</b>	
Somatostatin analogs	35 (31%)
Surgery	56 (50%)
Chemotherapy	40 (36%)
Interferon α	47 (42%)
Radio frequency ablation (liver metastases)	7 (6%)
External radiation therapy	2 (2%)
Hepatic artery chemoembolization	7 (6%)
Peptide receptor radionuclide therapy	18 (16%)

\*Lung carcinoids all had mitotic counts ≤ 10 and were accordingly placed in G1 or G2 groups.

be a clearly detectable lesion on the somatostatin receptor image to be counted as SRI-positive in the case of lesion discovery on the respective fused PET/CT or SPECT/CT images. CT data, masked for both SPECT and PET, were additionally evaluated by an experienced radiologist and used as a reference. The absolute number of lesions per organ system was obtained with a numeric

limitation of 10 lesions per organ and 30 positive findings for lymph nodes per patient.

Discrepant SRI findings—that is, foci that were recognized only on 1 of the 2 SRI methods—were classified as true-positive if they were positive on the CT-only assessment performed masked to PET and SPECT results but using the coregistered CT or were confirmed during later follow-up on biopsies, by the other SRI modality, or on additional imaging (CT or ultrasonography).

Maximum standardized uptake values were calculated for the lesion with highest tracer uptake in each organ obtained by drawing spheric volumes of interest sufficiently large to encompass the whole lesion—that is, including a rim of surrounding normal tissue.

Comparisons between the 2 methods were performed on the basis of patients, organs, and lesions. Sensitivity, specificity, and accuracy were calculated on a patient basis.

### Statistical Analyses

The McNemar test for paired proportions with continuity correction was applied to compare <sup>64</sup>Cu-DOTATATE and <sup>111</sup>In-DTPA-OC at the patient level. The 95% confidence intervals for sensitivity, specificity, accuracy, and predictive values were computed using the adjusted Wald method. A sign test was used to explore differences in lesion detection rates between the 2 SRI modalities. Two-sided *P* values of less than 0.05 were considered statistically significant.

## RESULTS

### Patient-Based Comparison

One hundred twelve patients underwent <sup>64</sup>Cu-DOTATATE PET, <sup>111</sup>In-DTPA-OC SPECT, and contrast-enhanced diagnostic CT in the inclusion period of 19 mo. In 100 of 112 NET patients, residual or recurrent disease was established on the basis of previous clinical evaluation, CT, and SRI within the scope of this study and prospective follow-up. Accordingly, 12 patients were negative for disease and of these 12, 8 were expectedly negative as they were newly operated on with removal of the known pathologic focus/foci and referred for evaluation of possible residual disease.

Eighty-seven patients were congruently positive on both <sup>64</sup>Cu-DOTATATE PET and <sup>111</sup>In-DTPA-OC SPECT scans. Ten patients with proven residual or recurrent disease were identified only by

**TABLE 3**  
Comparison of Diagnostic Performance of <sup>64</sup>Cu-DOTATATE and <sup>111</sup>In-DTPA-OC

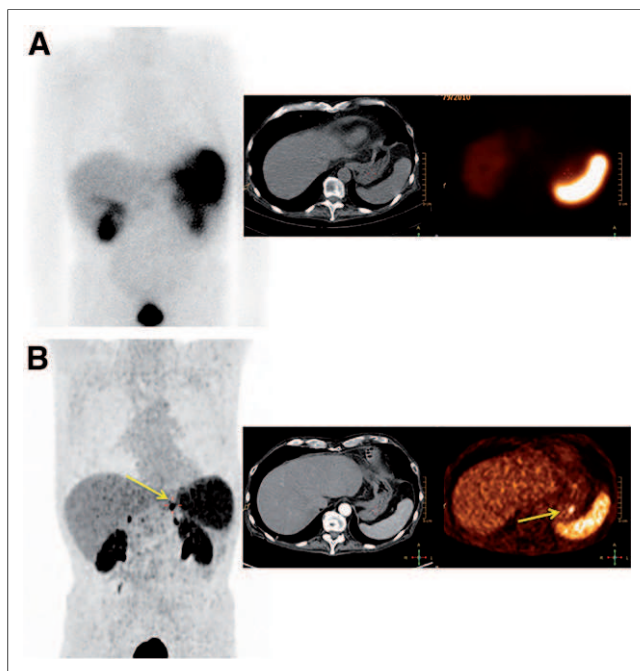
Parameter	<sup>64</sup> Cu-DOTATATE	<sup>111</sup> In-DTPA-octreotide
Sensitivity	97% (91%–99%)*	87% (79%–92%)*
Specificity	100% (96%–100%)	100% (96%–100%)
Accuracy	97% (92%–99%)*	88% (81%–93%)*
Positive predictive value†	100% (97%–100%)	100% (96%–100%)
Negative predictive value†	80% (54%–94%)	48% (30%–67%)

\**P* = 0.017; <sup>64</sup>Cu-DOTATATE vs. <sup>111</sup>In-DTPA-OC (McNemar test for paired proportions).

†At prevalence of disease of 89%.

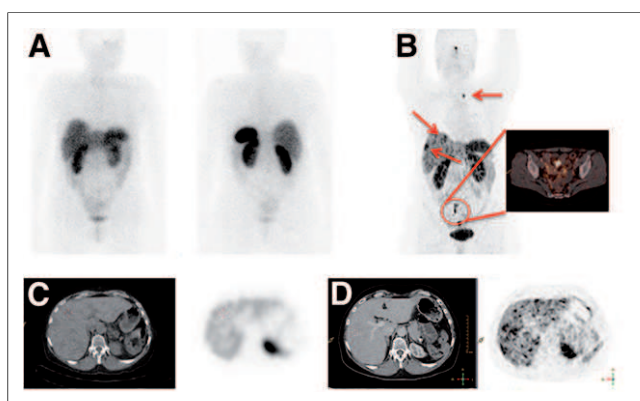
Numbers in parentheses are 95% confidence intervals calculated using adjusted Wald method.





**FIGURE 1.** Patient with gastric NET, which was not seen on  $^{111}\text{In}$ -DTPA-OC SPECT (Precedence scanner) (A) but was clearly visible (arrows) on  $^{64}\text{Cu}$ -DOTATATE PET (B). Likewise, CT did not reveal gastric NET, but biopsy confirmed it to be a true-positive finding.

$^{64}\text{Cu}$ -DOTATATE PET, leading to 97 true-positive  $^{64}\text{Cu}$ -DOTATATE PET cases and 87 true-positive  $^{111}\text{In}$ -DTPA-OC SPECT cases.  $^{111}\text{In}$ -DTPA-OC SPECT was false-negative in 13 patients, whereas  $^{64}\text{Cu}$ -DOTATATE PET was false-negative in 3 patients. Two of these 3 matching false-negative cases comprised patients with high-grade (G3) pancreatic NETs with liver metastases and Ki-67 indices of 40% and 30%, respectively. The third patient had been diagnosed with a bronchopulmonary carcinoid with a mitotic count of 1 and liver metastases. No false-positive results for either



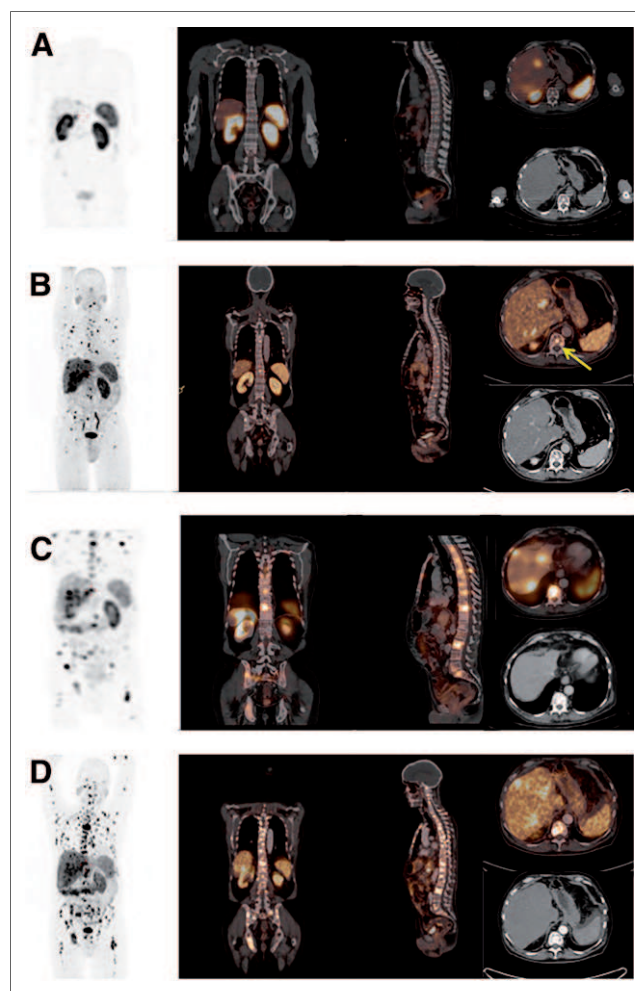
**FIGURE 2.** Multiple small liver metastases (>10), peritoneal solitary tumor mass, and 3 lymph node metastases shown on  $^{64}\text{Cu}$ -DOTATATE PET/CT in patient with pancreatic NET. No foci were detected by  $^{111}\text{In}$ -DTPA-OC SPECT (Precedence scanner). All findings on PET were confirmed to be true-positive. (A)  $^{111}\text{In}$ -DTPA-OC planar images. (B)  $^{64}\text{Cu}$ -DOTATATE maximum-intensity-projection image with arrows pointing at liver and lymph node metastases. Insert is fused PET/CT of peritoneal solitary tumor mass. (C) Axial CT and SPECT of liver. (D) Axial CT and PET of liver revealing several small liver metastases.

SRI modality were seen on a patient basis. Accordingly, sensitivity for  $^{64}\text{Cu}$ -DOTATATE and  $^{111}\text{In}$ -DTPA-OC was 97% and 87%, respectively. The comparison of diagnostic sensitivity, specificity, accuracy, positive predictive value, and negative predictive value and their 95% confidence intervals are shown in Table 3. The McNemar test revealed a statistically different performance of the modalities ( $P = 0.017$ ), with  $^{64}\text{Cu}$ -DOTATATE having a higher sensitivity and accuracy.

Five of the 10 patients with residual or recurrent NETs, which were revealed only by  $^{64}\text{Cu}$ -DOTATATE PET, had liver metastases. A typical case with discrepant PET and SPECT findings is shown in Figure 1.

Another example in which PET compared with SPECT identified 3 additional organs with tumor involvement is shown in Figure 2.

Of 112 included patients, bone metastases were present in 38 cases (34%) of which PET detected 36 and CT the remaining 2. All SPECT-positive cases were also PET-positive. In contrast, of the 36 PET-positive cases, 13 cases (29%) were SPECT-negative. Figure 3 shows a patient in whom multiple bone metastases were



**FIGURE 3.** Patient in whom PET identified more than 30 bone metastases whereas SPECT (VG Hawkeye scanner) identified only 1, and no bone lesions were visible on CT. During follow-up, multiple bone lesions could be identified on subsequent CT and SPECT scans but not until 2 y after lesions were found on the PET scan. (A)  $^{111}\text{In}$ -DTPA-OC from 2010. (B)  $^{64}\text{Cu}$ -DOTATATE from 2010; arrow marks bone metastasis. (C)  $^{111}\text{In}$ -DTPA-OC from 2012. (D)  $^{64}\text{Cu}$ -DOTATATE from 2012.

**TABLE 4**  
Organ-Based Analysis, Subgroup of 40 Patients with Discrepant Findings

Location of lesion	No. of additional PET positive findings*	Confirmation by Coregistered CT	CT	<sup>111</sup> In-octreotide	Biopsy	Not confirmed
Lungs	5	4				1
Liver	11	8	2	1		0
Bones	13	3	3	1		6
Lymph nodes	14	9	1	1		3
Carcinomatosis	3		2			1
Pancreas	5	3	2			0
Others†	7	3	2		1	1
Total	58	30	12	3	1	12

\*No. of PET foci does not equal no. of patients because some patients had more than 1 positive site.

†Others include 1 cerebral lesion, 1 peritoneal soft-tissue mass, 1 gastric lesion (primary), 1 chest wall lesion, 2 intestinal lesions (1 primary tumor), and 1 ovary lesion.

revealed by <sup>64</sup>Cu-DOTATATE in contrast to only 1 identified by <sup>111</sup>In-DTPA-OC.

In another case, PET identified the primary tumor in the terminal ileum and 1 abdominal lymph node metastasis whereas SPECT identified only the abdominal lymph node metastasis. The patient was subsequently operated on, and both foci were identified and removed.

#### Organ-Based Comparison

An organ-based analysis yielded concordant findings in 72 (64%) patients—that is, that both <sup>111</sup>In-DTPA octreotide and <sup>64</sup>Cu-DOTATATE PET consistently showed no lesions or consistently revealed at least 1 lesion for all organs/regions of the patient. In 40 of the 112 patients (36%), <sup>64</sup>Cu-DOTATATE PET detected lesions in additional organs/regions. There did not seem to be a difference in performance between the 2 SPECT scanners used, because there were 6 of the 21 patients (29%) scanned using the VG Hawkeye with discrepant findings in comparison to 34 of the 91 patients (37%) scanned using the Precedence scanner with discrepant findings. In some patients, 2 or more additional organ involvements were identified by PET, giving a total of 58 additional organ involvements found on PET compared with SPECT (Table 4). During the 42–60 mo of follow-up, the additional organ involvements identified on PET were confirmed to be true-positive in 35 of the 40 patients. Details on discrepant organ findings and how they were confirmed are given in Tables 4 and 5.

The most common discrepant finding was lymph node metastases. Thus, in 14 of the 40 discrepant cases, no lymph node metastases were present on SPECT whereas PET identified up to 11 lymph node metastases. Only in 2 of the 40 patients did SPECT identify more than 5 lymph node metastases whereas PET revealed more than 5 lymph node metastases in 13 cases.

In 11 patients, no liver lesions were present on SPECT whereas PET identified up to 20 liver metastases. In 3 of these 11 patients, the liver metastases were also not evident on CT, but all 3 were later confirmed to be true-positive lesions. In general for all 40 discrepant cases, PET identified at least as many and often more lesions than both SPECT and CT.

All lesions detected on <sup>111</sup>In-DTPA-OC SPECT were also detected on <sup>64</sup>Cu-DOTATATE PET. In 10 of the 40 cases, no

lesions were detected by SRS and in 5 of these patients the CT scans were also negative.

#### Lesion-Based Comparison

In total, 1,213 lesions were detected by <sup>64</sup>Cu-DOTATATE PET in comparison to 603 lesions detected by <sup>111</sup>In-DTPA-OC SPECT (Table 6). Of the 112 patients, 21 (19%) were scanned on the VG Hawkeye scanner, and in agreement with this, 123 (20%) of the 603 lesions detected by <sup>111</sup>In-DTPA-OC were identified using the VG Hawkeye scanner. In 28 patients (25%), PET and SPECT identified the same number of lesions; in 52 patients (46%), PET identified 1–9 more lesions than SPECT; and in 32 patients (29%), PET identified 10 or more additional lesions than SPECT. Tables 5 and 6 provide further details.

The most frequent finding was liver metastases, for which 468 lesions were present on PET, compared with 320 on SPECT. The clearest difference was the detection rate of bone metastases for which 208 lesions were found on PET, compared with 90 on SPECT.

#### DISCUSSION

In this prospective cohort study of 112 patients, we compared a new PET tracer, <sup>64</sup>Cu-DOTATATE, with the SPECT-based gold standard for imaging of somatostatin receptors in tumor lesions of NET patients (21,22). We found that the PET-based tracer was far superior to the current gold standard. With these results, we conclude that the <sup>64</sup>Cu-DOTATATE PET tracer can safely be implemented as a routine for diagnostic imaging of NET patients.

Recently, we developed and tested in a phase 1 study in 14 patients a new <sup>64</sup>Cu-based tracer, <sup>64</sup>Cu-DOTATATE, targeting somatostatin receptors (14). Although these initial results were most promising, a larger study is needed before implementing the tracer into clinical routine as replacement for <sup>111</sup>In-DTPA-OC (Octreoscan; Covidien). In line with this, we prospectively studied a larger series of 112 consecutive NET patients in a head-to-head comparison study. In the present study, we found that twice as many foci were identified. Still, whether 10 or 15 liver metastases are found is not necessarily important additional information. However, also when analyzing organ by organ, 58 additional organ systems were found to be involved in 40 patients when <sup>64</sup>Cu-DOTATATE was used, compared with <sup>111</sup>In-DTPA-OC, which could potentially be

**TABLE 5**  
Cases Showing Discrepant Results Between <sup>64</sup>Cu-DOTATATE PET and <sup>111</sup>In-Octreotide SPECT Scans

Identification no.	<sup>64</sup> Cu-DOTATATE PET	<sup>111</sup> In-DTPA-octreotide SPECT	Discrepant organ systems	Confirmed?
1	CARC (1), OSS (>10), LN (>30), PUL* (6)	CARC (1), OSS (1), LN (8)	PUL	Yes
2	MAM (>10), pSTM (1), LN (19), HEP* (>10) + OSS* (1)	MAM (>10), pSTM (1), LN (1)	HEP, OSS	Yes
3	HEP (1), pSTM (1), OSS* (3), LN* (2)	HEP (1), pSTM (1)	OSS, LN	Yes/OSS no
4 <sup>†</sup>	INT (1), HEP (>10), OSS (7), LN (6), CARC* (1)	INT (1), HEP (>10), OSS (4), LN (2)	CARC	Yes
5 <sup>†</sup>	LN (1), PANC* (3), PUL* (4)	LN (1)	PANC, PUL	Yes
6 <sup>†</sup>	HEP (1), pSTM (1), CARC (1), BRA* (1), OSS* (1)	HEP (1), pSTM (1), CARC (1)	BRA, OSS	Yes/OSS no
7 <sup>†</sup>	HEP* (1), INT (1), OSS (>20), LN (13)	INT (1), OSS (13), LN (2)	HEP	Yes
8	OSS* (1), LN* (4)	None	OSS, LN	Yes/OSS no
9	HEP (>10), pSTM (1), LN* (6)	HEP (>10), pSTM (1)	LN	Yes
10	HEP* (>10), pSTM* (1), LN* (3)	None	HEP, pSTM, LN	Yes
11	INT (1), LN* (1)	INT (1)	LN	No
12	HEP (>20), PANC (5), LN (4)*	HEP (>10), PANC (1)	LN	Yes
13	HEP (2), LN* (2)	HEP (1)	LN	Yes
14	STOMACH* (1), LN* (2)	None	Stomach, LN	Yes/LN no
15	HEP (7), pSTM (1), CARC* (1)	HEP (7), pSTM (1)	CARC	No
16	HEART/pericardium (4), pSTM (2), CARC (1), OSS (>10), chest wall* (1), LN* (11)	HEART/pericardium (1), pSTM (2), CARC (1), OSS (4)	Chest wall, LN	Yes
17	Heart/pericardium (2), HEP* (3), INT (1), pSTM (1), LN (>15)	Heart/pericardium (2), INT (1), pSTM (1), LN (1)	HEP	Yes
18	HEP* (>20), LN* (>10)	None	HEP, LN	Yes
19 <sup>†</sup>	PANC (1), HEP* (1)	PANC (1)	HEP	Yes
20	HEP (>10), PANC* (1), LN* (3)	HEP (>10)	PANC, LN	Yes/LN no
21	INT* (1), LN (1)	LN (1)	INT	Yes
22	HEP* (>10), LN (1)	LN (1)	HEP	Yes
23	INT* (3), PANC* (1)	INT (1)	PANC	Yes
24 <sup>†</sup>	HEP* (5), OSS* (1)	None	HEP, OSS	Yes
25	PUL* (1), LN (1), OSS* (1)	LN (1)	PUL, OSS	Yes/OSS no
26	HEP (2), pSTM (2), OSS* (10), LN (17)	HEP (2), pSTM (2), LN (7)	OSS	Yes
27	CARC (2: hepatic, peritoneal), OSS* (5)	CARC (2: hepatic, peritoneal)	OSS	Yes
28	INT (1), LN* (1)	INT (1)	LN	Yes
29	PLEURA (4), HEP* (>10), PANC* (1), OSS (>10), LN (1)	PLEURA (2), OSS (3), LN (1)	HEP, PANC,	Yes
30	HEP* (8)	None	HEP	Yes
31	HEP* (3), PANC* (1), OSS* (3)	None (neither primary)	HEP, PANC, OSS	Yes
32	PUL* (2), HEP (>10), INT* (1), pSTM (1), OSS (6), LN* (1)	HEP (4), pSTM (1), OSS (1)	PUL, INT, LN	Yes/INT no
33	PUL* (1), OVAR (1), LN (17)	OVAR (1), LN (3)	PUL	No
34	OVAR* (1)	None	OVAR	Yes
35	INT (1), pSTM (1), CARC* (1)	INT (1), pSTM (1)	CARC	Yes
36	PUL (1), HEP (>10), OSS* (2)	PUL (1), HEP (>10)	OSS	Yes
37	PANC (1), HEP (>10), OSS* (1)	PANC (1), HEP (4)	OSS	No
38	LN* (7)	None	LN	Yes
39	HEP (>10), OSS* (2), LN (5)	HEP (6), LN (3)	OSS	Yes
40	OSS* (2)	None	OSS	Yes

\*Not seen on <sup>111</sup>In-DTPA octreotide.

<sup>†</sup>Patient scanned on VG Hawkeye scanner.

CARC = carcinomatosis; OSS = osseous; LN = lymphatic; PUL = pulmonary; MAM = mammary; pSTM = peritoneal soft-tissue mass; HEP = hepatic; INT = intestinal; PANC = pancreatic; BRA = brain; OVAR = ovarian.



TABLE 6

Comparison of Absolute Number of Lesions Detected by PET and SPECT Based on Organ Location

Location	<sup>64</sup> Cu-DOTATATE PET (absolute no.)	<sup>111</sup> In-octreotide SPECT (absolute no.)	P
Brain	1	0	NA
Lungs	27	5	<0.0001
Liver	468	320	<0.0001
Stomach	1	0	NA
Small intestine	19	15	NS
Peritoneal soft-tissue mass	33	25	NS
Pancreas	25	12	0.0078
Carcinomatosis	14	11	NS
Other locations	4	3	NS
Bones	208	90	<0.0001
Soft tissue	21	14	NS
Lymph nodes	392	108	<0.0001
Total	1,213	603	

NA = not applicable; NS = not significant.

of importance for the prognosis (23,24) and treatment selection (25–28). Nevertheless, more foci found by PET are not necessarily representative of true-positive foci. Therefore, we performed a long follow-up to be able to evaluate whether foci were true-positive or false-positive. With a follow-up of 42–60 mo, we found that 46 (79%) of the 58 discrepant findings could be evaluated as true-positive on PET, and in no case were PET findings false-positive.

Accordingly, <sup>64</sup>Cu-DOTATATE performs better than <sup>111</sup>In-DTPA-OC because it detects more regions truly involved in the disease. When better performance is additionally accompanied by a lower radiation dose of 6.3 mSv (14,29) and an easier workflow, for example, a 1-d instead of 2-d procedure, we do not hesitate to recommend implementing this technique in our routine as a replacement for <sup>111</sup>In-DTPA-OC.

It may be argued that <sup>68</sup>Ga-based tracers such as <sup>68</sup>Ga-DOTATATE, <sup>68</sup>Ga-DOTATOC, or <sup>68</sup>Ga-DOTANOC would equally perform better than <sup>111</sup>In-DTPA-OC (30). Indeed, such comparative studies also found more foci identified with <sup>68</sup>Ga-based tracers than with SPECT (27,31,32). These studies on average found 30% (27,32,33) more foci using PET than SPECT. Compared with our study in which we found a higher percentage of additional lesions (50%), it seems we could have a better detection rate. Moreover, <sup>64</sup>Cu-DOTATATE found several lesions not detected on CT scans, which is less commonly reported for the <sup>68</sup>Ga-labeled tracers (32,34,35), which could easily be explained by the better resolution obtained when using <sup>64</sup>Cu than <sup>68</sup>Ga due to the 4-fold-lower positron range of <sup>64</sup>Cu. Moreover, in contrast to our study with <sup>64</sup>Cu, most of the <sup>68</sup>Ga studies did not rigorously perform a long-term follow-up to establish whether the additional foci were true-positive.

It could be asked how our tracer would perform in a head-to-head comparison with <sup>68</sup>Ga-based somatostatin receptor tracers.

Currently we do not know this, and because only a study also including a long-term follow-up can answer which tracer is best, such a study is not yet available. However, with <sup>111</sup>In-DTPA-OC still being the most commonly used tracer, in particular in the United States, we find our current study timely and of clinical relevance.

## CONCLUSION

With detection of twice as many lesions, identification of disease involvement in organs not previously identified in one third of enrolled patients, and a favorable dosimetry and workflow, we have demonstrated that <sup>64</sup>Cu-DOTATATE is far superior to <sup>111</sup>In-DTPA-OC. Accordingly, we do not hesitate to recommend implementation of this technique in our routine as a replacement for <sup>111</sup>In-DTPA-OC.

## DISCLOSURE

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## **$^{64}\text{Cu}$ -DOTATATE PET for Neuroendocrine Tumors: A Prospective Head-to-Head Comparison with $^{111}\text{In}$ -DTPA-Octreotide in 112 Patients**

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